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The principal goal was to understand why breast cancer cells are able to evade the host immune system despite the presence of tumor antigens and tumor antigen-specific T lymphocytes. We had previously demonstrated that tumor-derived prostaglandin E_2 (PGE_2) directly contributes to the lack of a significant immune response to breast cancer cells. However, the production of PGE_2 by breast cancer cells did not completely explain the immune suppressive effect of breast cancer cells. We have subsequently demonstrated that GA733-2/mEGP, a type I cell surface breast cancer protein, is able to efficiently block the presentation of a variety of antigens from dendritic cells (DC). Murine DC expressing mEGP were unable to stimulate allogeneic T cell responses or responses to model tumor antigens. T cell inhibition is the result of a direct effect on the DC. When mEGP or GA733-2 was provided to the T cell stimulation assay in the form of tumor debris, T cell activation was also inhibited. We postulate that mEGP blocks antigen loading into MHC complexes are further pursing the mechanism of action.

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TABLE OF CONTENTS

Human breast cancer derived PGE_2 inhibits B7-1 induced T cell proliferation

Key words: breast cancer, immunotherapy, immunosuppressive factors, GA733-2, mEGP, antigen presentation

INTRODUCTION

The principal goal of this study is to understand why breast cancer cells are able to evade the host immune system despite the presence of tumor antigens and tumor antigen-specific T lymphocytes. We postulated that the production of prostanoids, principally prostaglandin E_2 (PGE_2), by the tumor directly contributes to the lack of an immune response to breast cancer cells. As reported year we conducted experiments to show that human breast cancer cells secrete soluble agents that directly inhibit T lymphocytes. We demonstrated that one of the major inhibitory factors made by breast cancer cells is PGE_2. This demonstrates that an important function of PGE_2 is to directly alter or suppress the immune response to breast cancer cells. We showed that the expression of cyclooxygenase (COX) and the resultant production of PGE_2 are sufficient to abrogate the T cell response to tumor cells in a vaccination model. The initially proposed first year Aims and related Tasks were largely completed as described in last year's report. In brief, we reported on breast cancer cells inability to stimulate T cell proliferation due to the release of immunosuppressive factors by these tumor cells. In support of this hypothesis we observed that conditioned media (CM) obtained from breast cancer cell lines inhibited the proliferation of mononuclear cells. PGE_2 was shown to be an important contributor to the T cell inhibitory effect of breast cancer CM. Several lines of evidence supported this conclusion. Indomethacin treatment of MCF-7 cells reduced PGE_2 production and partially alleviated inhibition of MN cell proliferation. Indomethacin did not completely remove the inhibitory effect, which is consistent with the presence of residual PGE_2 that could be detected by LC-MS. More conclusive evidence for the involvement of PGE_2 in T cell growth inhibition was obtained when we removed PGE_2 from CM using an affinity column that specifically binds PGE_2. The selective elimination of PGE_2 from MCF-7 CM removed its MN cell growth inhibitory activity completely. Thus, inhibition of MN cell proliferation is mediated, at least in large part, by PGE_2 produced by MCF-7 cells. We also noted that the amount of PGE_2 production did not linearly correlate with inhibition of the proliferation of stimulated MN cells. CM from the immortalized, non-tumorigenic human breast epithelial cell line HBL-100 produced significant levels of PGE_2 (more than MCF-7) but did not suppress MN cell proliferation. Similarly, the CM from two cell lines (SUM149PT and SUM190PT) that produced the most PGE_2 showed only moderate inhibition of MN cell proliferation. Based on these results it appeared likely that other breast cancer factors likely contributed to the immunosuppressive effect. In support of this notion we found that BT-20 cells did not produce significant amounts of PGE_2 but inhibited PHA-dependent proliferation of MN cells by 41%. This suggests that other tumor-derived factors may induce immunosuppression as previously reported. Taken together these data suggest that PGE_2 is a necessary but not always sufficient cofactor of tumor-derived immunosuppression and likely act in concert with other factors. These data suggested that PGE_2 derived from human breast cancer cells can contribute to inhibition of cellular immunity but it remained unclear how to mediate reversal of tumor-induced immunosuppression as part of cancer therapy given the complexity and heterogeneity of tumor mediated immune suppression.

BODY OF REPORT

At this point in our investigations we had proposed to pursue Specific Aim 2. We proposed to determine whether inhibition of prostaglandin synthesis in vivo enhances the immunogenicity of murine mammary tumors in vivo. We proposed to use homologous recombination methods to prepare COX knockout cell lines from SCK, T2994 and/or MT901 cells using methods that had been previous described for the COX-knockout mice. However, two major obstacles prevented the pursuit of this objective. First, it became apparent that somatic cell knockout cell lines could not be prepared as proposed due to the aneuploid and unstable karyotype of the cell lines that we had available for this purpose. This was in fact alluded to by our reviewers at the time of the proposal submission. Secondly, even if COX null cell lines were prepared it would be difficult to assess the relative contribution of PGE2 to immunosuppression given our previous observations that PGE_2 was but one of several factors that contribute to immune suppression. The single-minded pursuit of PGE_2 as a therapeutically targetable factor in breast cancer progression seemed unsupportable. Therefore, we altered our approach and decided to improve our understanding of other factors that, along with PGE_2, contributed to immune suppression. Thus, the proposed tasks 8 through 11 were not pursed since the represented unachievable goals based on the best available information. We have gone on to characterize the previously unreported immunosuppressive effects of a well-known tumor antigen GA733-2 (also known as mEGP in the mouse).

GA733-2 is a type I transmembrane protein glycoprotein protein that is expressed on breast cancer cells and on some normal tissues [1]. The role of this protein is not well understood, although it has been postulated to be an adhesion molecule [2]. Our preliminary work has focused on the murine homologue of GA733-2 called mouse epithelial glycoprotein (mEGP). The mEGP protein has 82% sequence homology to GA733-2 and a similar tissue distribution [3, 4]. We believe that our preliminary data in the murine system provides direct and compelling evidence to support the study of the human protein in *in vitro* models. We have found that the mEGP is expressed on spontaneously occurring mouse mammary tumor cells such as the SCK cell line which arose naturally from an A/J mouse [5], and the NT5 cell line which was derived from spontaneous mammary tumors arising in the HER2/neu FVB trangenic mouse. In contrast, chemically induced murine mammary tumor cell lines do not (e.g., MT901 & T2994 lines; our unpublished data). GA733-2 has been shown to be expressed on human breast cancer cell lines although the role of GA733-2 in breast cancer is unknown [1, 6, 7]. The similarity of the mEGP and GA733-2 sequences and the expression of GA733-2 and mEGP on human breast and mouse mammary tumors, respectively, strongly suggest that the biologic behavior of the murine protein will predict the behavior of the human protein.

mEGP Blocks Class II Restricted Antigen Presentation in Murine Dendritic Cells. In a series of in vitro experiments we have established that mEGP: (1) blocks antigen presentation in mixed lymphocyte reaction (MLR) and MHC class II restricted antigen-specific T cells activation; (2) inhibits T cell activation by direct action on the antigen presenting cell (APC) and not by directly inhibiting the T cells; and (3) can inhibit dendritic cells (DC) either when expressed in the DC (from a transfected gene) or when the DC takes up the mEGP protein from the external environment. These data strongly suggest that one function of the mEGP and GA733-2 molecules are to block MHC class II presentation of tumor-derived antigens as shown in figure 1.

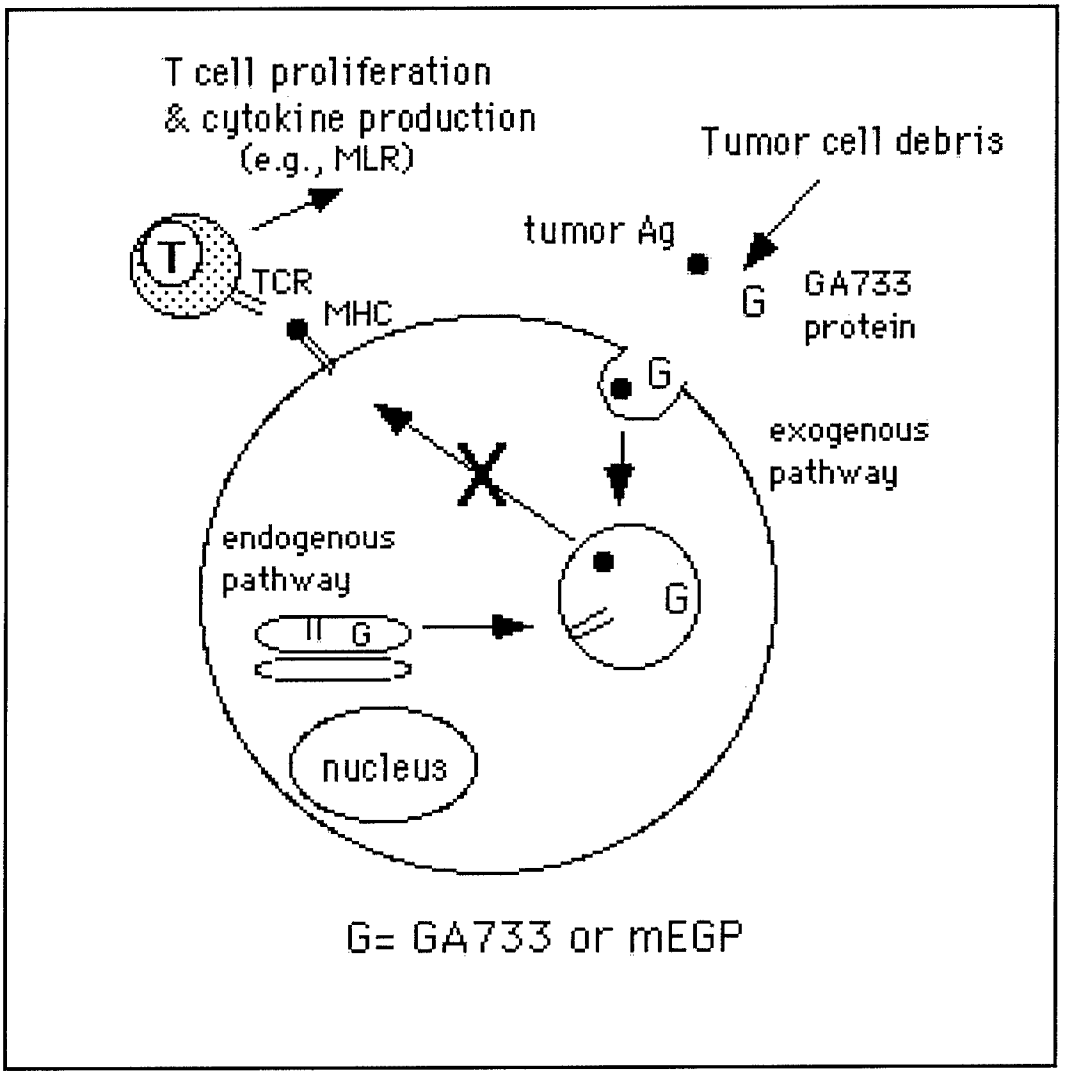

Figure 1. Endogenously synthesized (adenoviral vector delivered) mEGP or GA733-2 (G) traffics to the endosome from the endoplasmic reticulum. Endocytosed mEGP or GA733-2 (G) is taken up by the same pathway tumor antigens enter the DC. We hypothesize that in the endosome mEGP/GA733-2 is able to block formation of the peptide-MHC (class II) complex and thereby block the MLR. By this mechanism, exogenous GA733-2 from breast cancer cells would be taken up with tumor antigens and block their presentation to CD4+ T cells.

mEGP blocks antigen presentation in mixed lymphocyte reaction (MLR) and in antigen specific T cells activation. Our central model has been the MLR, where allogeneic T cells are activated by bone marrow-derived dendritic cells (BMDC). When BMDC from BALB/c mice are mixed with C3H derived purified T cells, T cell proliferation (as measured by ^{3}H-thymidine incorporation) increases as a function of the number of murine BMDC (fixed number of T cells, see figure 2). The level of ^{3}H-thymidine incorporation is unaltered by transfection of the BMDC with a control adenovirus (Ad.Bgl2, no transgene) or with an adenovirus expressing GA733-2 (Ad.GA733). However, transfection of the murine BMDC with an adenovirus expressing mEGP (Ad.mEGP) completely blocks the MLR response (figure 2, and figure 1, endogenous pathway of mEGP/GA733-2 entry into endosome). This is also seen when other MHC-disparate combinations of murine BMDC and T cells were used (not shown). In addition, the control culture and those containing BMDC transfected with Ad.GA733 or Ad.Bgl2 produce identical amounts of IL-2, IFNγ IL-10 and IL-4, whereas the MLR contain the mEGP expressing BMDC fail to induce production of these cytokines (not shown). These data suggest that T cell activation fails to occur when mEGP is expressed in the BMDC. Both the BMDC and the T cells remain viable in the mEGP-containing MLR as evidence by: (1) the microscopic appearance of the cells in culture (with and without trypan blue); (2) the production of IL-12 (BMDC derived) was the same in all of the MLRs including the mEGP-containing cultures; and (3) the ability of added anti-CD3 or ConA to induce T cell proliferation when added to the mEGP-containing MLR (not shown). Thus, the absence of T cell proliferation and cytokine production in the present of mEGP is not due to cell death or other non-specific causes. These and additional data suggest that mEGP inhibits T cell proliferation by direct action on the antigen presenting cell (APC) and not by directly inhibiting the T cells. To confirm these findings in different model systems, we used T cells from transgenic mice expressing class II restricted T cell receptors (TCR) specific for either ovalbumin (OVA) or hen egg lysozyme (HEL) antigens. Using the same experimental design as employed for the MLR above, we found that BMDC pulsed with OVA or HEL proteins were unable to initiate antigen specific T cell activation of their respective trangenic T cells when mEGP (but not controls) was expressed in the stimulating dendritic cells (not shown). Both the OVA and HEL models are models of class II restricted antigen presentation. These data substantiate the ability of mEGP to block T cell responses to relevant antigens. We have also found (not shown) that murine class II restricted T cell hybridomas specific for OVA failed to respond to DC expressing mEGP, whereas murine class I restricted T cell hybridomas specific for OVA did respond to DC expressing mEGP (hybridomas provided by Dr. Kenneth Rock). This confirms the class II restricted effects of mEGP inhibition of the MLR.

mEGP can inhibit T cell activation when the APC takes up the mEGP protein from the external environment. To determine whether tumor cell-derived mEGP (or GA733-2) could block APC function, we repeated the MLR experiment and added tumor cell debris containing mEGP (exogenous pathway of mEGP/GA733-2 entry into endosome, figure 1). FBL cells (mEGP and GA733-2 negative, data not shown) were transfected with control adenovirus (Ad.Bgl2) or the adenovirus expressing mEGP (Ad.mEGP). The FBL cells were pelleted from their tissue culture media then lysed by repetitive freeze thawing. As shown in figure 3, BALB/c BMDC induce proliferation of allogeneic (C3H) T cells as shown in figure 3. When increasing amounts of mEGP^{+}-FBL3 cell debris (as measured by protein concentration) was added to the MLR, T cell proliferation was suppressed. This was not seen in the controls where increasing amounts of mEGP^{-}-FBL3 cell debris was added. These data suggest that exogenous mEGP protein can block the MLR in the same manner as endogenous mEGP (produced by adenovirus transfection of BMDC). The same effect has been seen when purified recombinant mEGP

protein (produced in bacteria as a GST fusion protein) was added to the MLR (not shown). Both endogenously and exogenously produced mEGP converge in the endosome: the site of MHC class II loading (figure 1). Therefore, we hypothesize that mEGP/GA733-2 inhibits the MLR by acting in the endosomal compartment. These data demonstrate that tumor cell derived mEGP can block T cell activation and suggests that mEGP and its human homolog GA733-2, can serve to block T cell activation in the tumor microenvironment. Our data suggest that the breast tumor infiltrating DC may be inactivated, with respect to class II antigen presentation, following encounter with the tumor cell debris (e.g., apoptotic bodies). APC (DC) within the tumor would be expected to engulf tumor debris including tumor-associated antigens for processing. However, in the process of taking up tumor-associated antigens, the APC would be expected to also take up mEGP or GA733-2, which is highly abundant. In doing so, we postulate that the DCs can no longer effectively present the tumor antigens. We are currently pursuing the mechanism by which mEGP blocks antigen presentation in our mEGP/mouse model systems. The murine system is well suited for such mechanistic studies because of the availability of unique immunologic reagents. However, at this juncture, it is critical to establish that the human protein has a similar function in patients with breast cancer. We postulate that GA733-2 contributes to the failure of the immune system to recognize breast tumor antigens, and potentially to the overall immune suppression seen in patients with advanced metastatic breast cancer.

Human GA733-2 blocks a human MLR. We performed a single preliminary experiment where adenovirus expressing GA733-2 was used to transduced human PBMCs for use as APCs. Using unactivated PBMCs (no IL-4, GM-CSF, etc.) GA733-2-PBMCs failed to elicit a MLR under conditions where Ad.Bgl2 transduced PBMC and control APCs did elicit an MLR response (Figure 4). The mEGP-MLR was suppressed to approximately 50% the extent of the GA733-2-MLR suggesting that while GA733-2 is inactive in the mouse model, the murine protein may have some activity in the human model. However, the use of PBMCs in this manner is difficult since they require very high amounts of adenovirus (MOI of 10,000) as they are not easily or completely transduced by adenovirus vectors. For this reason we propose to use in this proposal PBMC derived DC as APCs which are easily transduced by adenoviral vectors.

Homology between mEGP and Invariant chain (Ii). In the course of these studies we sought to identify homology between mEGP and other proteins that might shed light on its function. mEGP contains a thyroglobulin domain, which is a structural element first found in thyroglobulin and characterized by the sequence motif Cys-Trp-Cys-Val [8]. Similar domains have been described in other proteins including the p41 form of invariant chain [9] and equistatin (a protein derived from sea anemone, [10, 11]. In p41 invariant chain and in equistatin it has been shown that the thyroglobulin domain acts as an inhibitor of cysteine proteases. p41 invariant chain inhibits cathepsin L, but not cathepsin D [12-15], equistatin inhibits cathepsin D, B, and L as well as papain [11]. The example of equistatin, which contains three thyroglobulin domains, illustrates that subtle differences in thyroglobulin domains have significant implications for their function. Although the three thyroglobulin domains of equistatin have similar amino acid sequences, they inhibit different proteinases [11]. The presence of a thyroglobulin domain in mEGP suggested that mEGP might play a role in regulating cathepsin activity. In the context of antigen presentation, the cathepsin proteases in the endosomal and lysosomal compartment are known to play a critical role [16]. For example, cathepsin L and S are necessary for the late stages of invariant chain degradation in the thymic cortex [17], and in the thymic medulla and in peripheral APC, respectively [18]. Cathepsins are also thought to mediate antigen

processing into peptides, and a balance of protease activity seems to be necessary for efficient antigen presentation to fully degrade invariant chain but to prevent enzymatic destruction of antigen determinants [15]. It has been shown that p41 invariant chain, which blocks cathepsin L function, can increase MHC class II antigen presentation in a subset of antigens [19]. By comparison, if cathepsin S is blocked in APCs by an inhibitor or is absent (e.g., in knockout mice), the ability of MHC class II complexes to load and present antigen is impaired [20-22]. To assess the effect of mEGP on cathepsin activity in dendritic cells, we used a fluorometric assay [15]. The metabolism of the substrate used was increased in the mEGP transfected cells (Figure 5). The specificity of this increase is demonstrated by the ability of a known cathepsin-specific inhibitor to reverse block the rise in cathepsin activity. Thus, mEGP appears to activate cathepsins. This could occur by either direct interaction of mEGP with cathepsin or indirectly by blocking a negative regulator of cathepsin activity (e.g., a p41fragment). Since cathepsins are crucial for the degradation of Ii and blockage of cathepsin S results in loss of Ag presentation in dendritic cells, we went on to perform pulse chase experiments to analyze the effect of mEGP on invariant chain and MHC class II proteins.

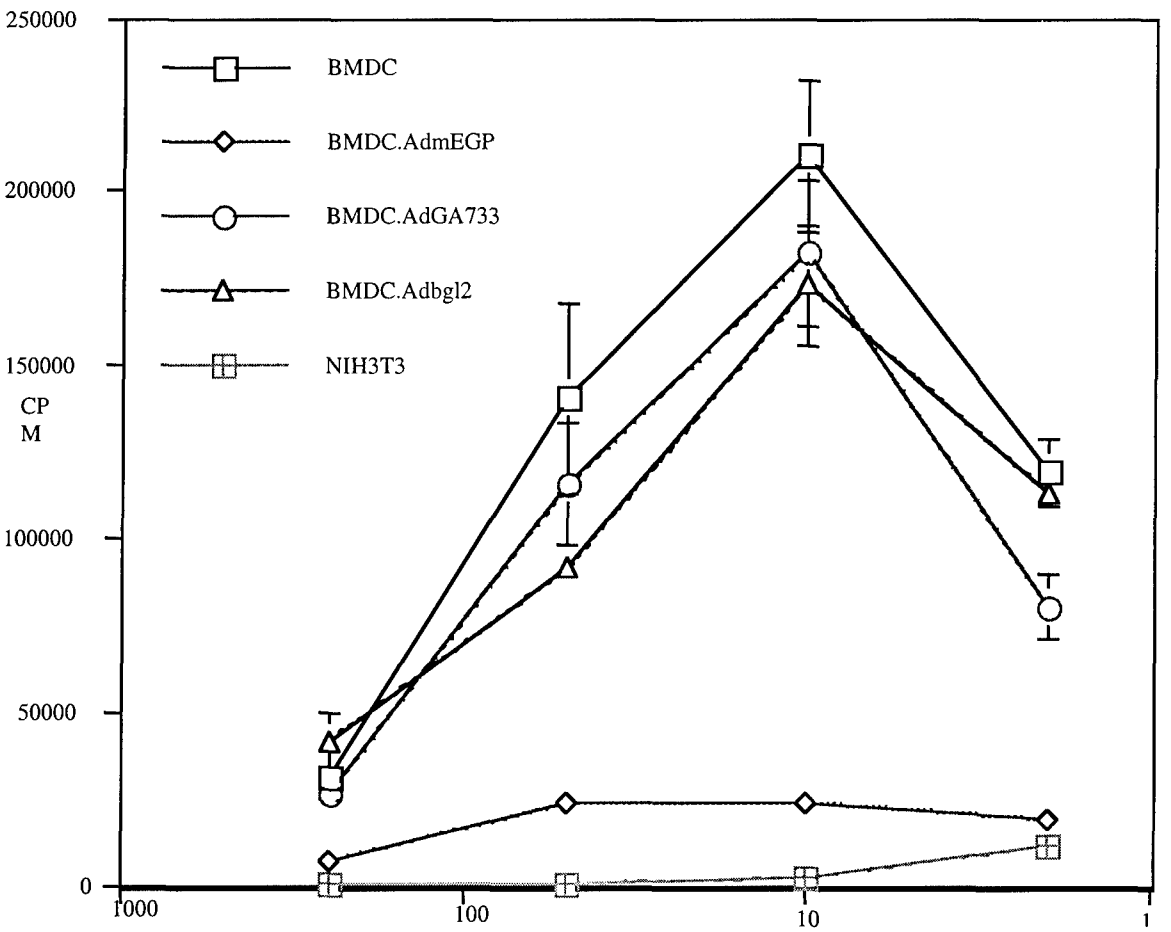

Figure 2. (above) Mouse MLR. BMDC expressing mEGP (◇) fail to elicit T cell proliferation, under conditions where BMDC expressing GA733-2 (○) or control BMDC (□) elicit T cell proliferation. NIH3T3 fibroblasts (⊠) serve as a negative control. Ad.Bgl2 transfected BMDC (△,only adenoviral proteins made) serves as an additional control

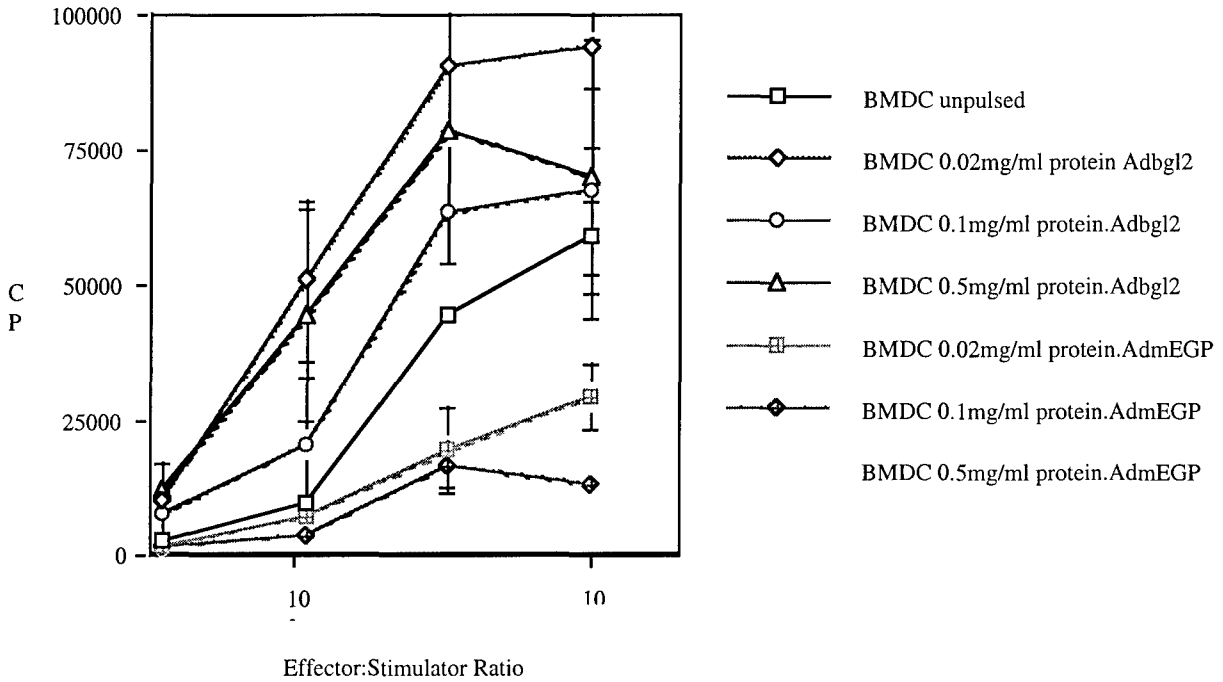

Figure 3. Addition of tumor cell debris containing mEGP protein to BMDCs blocks MLR. FBL cells (mEGP and GA733 negative) were transfected with control adenovirus (Ad.Bgl2) or the adenovirus expressing mEGP (Ad.mEGP). The FBL cells were pelleted from their tissue culture media then lysed by repetitive freeze thawing. BALB/c untreated BMDC (□) induce proliferation of allogeneic (C3H) T cells (compare with figure 2). When increasing amounts of $mEGP^{+}$-FBL cell debris (as measured by protein concentration) was added to the MLR, T cell proliferation was suppressed (hatched □,◇ & ○). This was not seen in the controls where increasing amounts of $mEGP^{-}$-FBL cell debris was added (open □,◇ & ○). These data suggest that exogenous mEGP protein can block the MLR in the same manner as endogenous mEGP (produced by adenovirus transfection of BMDC).

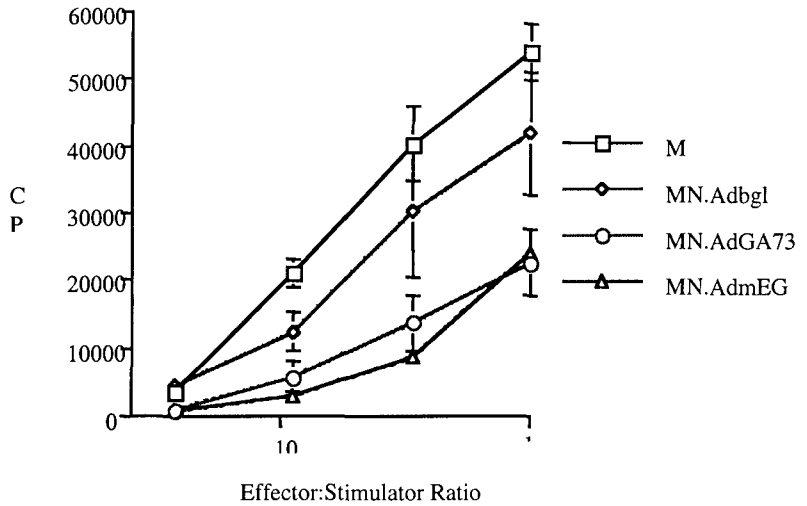

Figure 4. Human PBMCs as APC with allogeneic T cells in a *human* MLR. PBMCs with or without Ad.Bgl2 induce T cell proliferation (◇,□ respectively). PBMCs transduced with Ad.GA733 or Ad.mEGP inhibit the MLR when approximately 40% of the cells express GA733 or mEGP respectively.

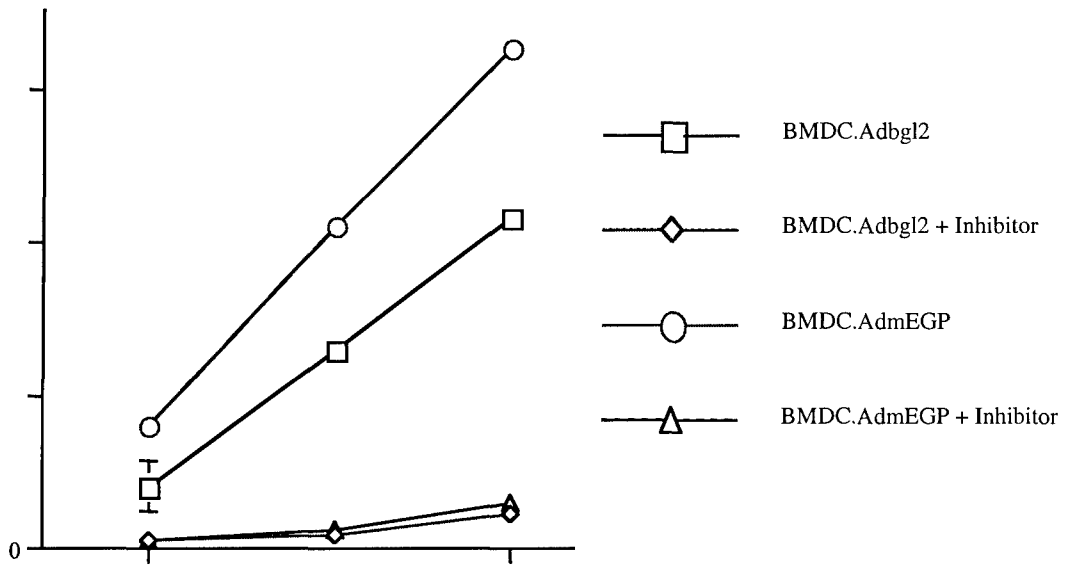

Figure 5. The effect of mEGP on Cathepsin Activity in DC. Increasing numbers of dendritic cells (10^4 to 10^5) were incubated with 120uM of the cathepsin-specific fluorogenic substrate 7-amino-4-methylcoumarin-carbobenzoxy-Phe-Arg (Peninsula Laboratories, Belmont, CA) in the absence or presence of 25uM Z-Phe-Ala-CH_2F, a cysteine protease inhibitor (Enzyme Systems, Livermore, CA). Assays were conducted for 60 minutes at 37°C in 100ul PBS. Enzyme activity was determined by quantitating the fluorescence released on hydrolysis of the substrates using a multi-well plate reader (Rainbow, Austria) adjusted at an excitation wavelength of 360nm and an emission wavelength of

460nm. Enzymatic activity is directly proportional to the number of DC (amount of enzyme), completely inhibited by a specific inhibitor, and increased in the presence of mEGP

KEY RESEARCH ACCOMPLISHMENTS

These studies demonstrate that:

1. mEGP when ectopically expressed in BMDC blocks an allogeneic "mixed lymphocyte reaction" (MLR) as assessed by T cell proliferation, IL-2 production and interferon-γ production.
2. Inhibition of T cell activation by mEGP is dose dependent, and exhibits no "trans" effect.
3. T cell activation in the MLR is restored in the presence of mEGP when Con A or anti-CD3 antibody is added to the MLR, however, antibodies to mEGP do not restore T cell responses.
4. mEGP blocks the response of lymphocytes with transgenic T cell receptors for OVA and HEL both when the intact protein is used as the antigen or when the specific class II restricted peptide is used as the antigen.
5. mEGP is able to block class II but not class I restricted presentation of OVA antigen.
6. mEGP when provided in the form of a lysed tumor cell expressing mEGP is also able to block T cell activation as assessed in both the MLR and OVA model experiments.
7. A truncated form of mEGP lacking the cytoplasmic domain is not able to block T cell activation when expressed in the BMDC but is able to block T cell activation when provided in tumor cell debris. This also holds true for the human antigen GA733.
8. mEGP does not alter BMDC morphology, cell surface expression of key T cell stimulatory molecules (e.g., B7-1, B7-2, class I, class II, CD 11b, CD 11c), production of IL-12 and overall viability.

REPORTABLE OUTCOMES

1. A manuscript is being prepared for submission to Nature Medicine.
2. Our finding that proteins in the membrane of breast tumor can inhibit an immune response is the basis of a RO1grant application to further pursue this finding. "Inhibition of T cells by a Breast Tumor Assoc. Antigen", NCI, reviewed in 1999 with a percentile ranking of 7%. A notice of award has not as yet been received pending congressional approval of the NIH budget.

CONCLUSIONS

We have provided evidence that tumor-derived PGE_2, limits the immune response to breast cancer cells in an experimental model. In addition, certain membrane proteins in breast cancer cells (GA733-2 antigen) appear to block T cell responses by indirectly interfering with antigen presentation by professional antigen presenting cells..

REFERENCES

1. Braun, S., F. Hepp, H.L. Sommer, et al., Tumor-antigen heterogeneity of disseminated breast cancer cells: implications for immunotherapy of minimal residual disease. Int J Cancer, 1999. **84**(1): p. 1-5.
2. Basak, S., J. Zaloudik, M. Nebit, et al. Mouse model of active immunotherapy against the human colon carcinoma-associated antigen CO17-1A/GA733. in Proceedings of th American Association for Cancer Research. 1996. Washington, D.C.: American Association for Cancer Research.
3. Litvinov, S.V., M.P. Velders, H.A. Bakker, et al., Ep-CAM: a human epithelial antigen is a homophilic cell-cell adhesion molecule. J Cell Biol, 1994. **125**(2): p. 437-46.
4. Bergsagel, P.L., C. Victor-Kobrin, C.R. Timblin, et al., A murine cDNA encodes a pan-epithelial glycoprotein that is also expressed on plasma cells. Journal of Immunology, 1992. **148**(2): p. 590-6.
5. Coughlin, C., M. Wysocka, H. Kurzawa, et al., B7-1 and IL-12 synergistically induce anti-tumor immunity. Cancer Res., 55:4980-87, (1995).
6. Braun, S. and K. Pantel, Biological characteristics of micrometastatic carcinoma cells in bone marrow. Curr Top Microbiol Immunol, 1996. **213**(Pt 1): p. 163-77.
7. Adkins, J.C. and C.M. Spencer, Edrecolomab (monoclonal antibody 17-1A). Drugs, 1998. **56**(4): p. 619-26; discussion 627-8.
8. Malthiery, Y., S. Lissitzky, , et al., Primary structure of human thyroglobulin deduced from the sequence of its 8448-base complementary DNA. European Journal of Biochemistry, . **165**(3): p. 491-8.
9. Strubin, M., C. Berte, and B. Mach, Alternative splicing and alternative initiation of translation explain the four forms of the Ia antigen-associated invariant chain. EMBO J., 1986. **5**: p. 3483-3488.
10. Lenarcic, B., A. Ritonja, B. Strukelj, et al., Equistatin, a new inhibitor of cysteine proteinases from Actinia equina, is structurally related to thyroglobulin type-1 domain. J. Biol. Chem., 1997. **272**(21): p. 13899-903.
11. Lenarcic, B. and V. Turk, Thyroglobulin type-1 domains in equistatin inhibit both papain-like cysteine proteinases and cathepsin D. J. Biol. Chem., 1999. **274**(2): p. 563-6.
12. Bevec, T., V. Stoka, G. Pungercic, et al., Major histocompatibility complex class II-associated p41 invariant chain fragment is a strong inhibitor of lysosomal cathepsin L. J Exp Med, 1996. **183**(4): p. 1331-8.
13. Bevec, T., V. Stoka, G. Pungercic, et al., A fragment of the major histocompatibility complex class II-associated p41 invariant chain inhibits cruzipain, the major cysteine proteinase from Trypanosoma cruzi. FEBS Lett, 1997. **401**(2-3): p. 259-61.
14. Fineschi, B. and J. Miller, Endosomal proteases and antigen processing. Trends Biochem. Sci., 1997. **22**(10): p. 377-82.
15. Fineschi, B., K. Sakaguchi, E. Appella, et al., The proteolytic environment involved in MHC class II-restricted antigen presentation can be modulated by the p41 form of invariant chain. J Immunol, 1996. **157**(8): p. 3211-5.
16. Cresswell, P., Proteases, processing, and thymic selection [see comments]. Science, 1998. **280**(5362): p. 394-5.
17. Nakagawa, T., W. Roth, P. Wong, et al., Cathepsin L: critical role in Ii degradation and CD4 T cell selection in the thymus. Science, 1998. **280**(5362): p. 450-3.

18. Pierre, P. and I. Mellman, Exploring the mechanisms of antigen processing by cell fractionation. Curr Opin Immunol, 1998. **10**(2): p. 145-53.
19. Peterson, M. and J. Miller, Antigen presentation enhanced by the alternatively spliced invariant chain gene product p41. Nature, 1992. **357**(6379): p. 596-8.
20. Riese, R.J., R.N. Mitchell, J.A. Villadangos, et al., Cathepsin S activity regulates antigen presentation and immunity. J Clin Invest, 1998. **101**(11): p. 2351-63.
21. Nakagawa, T.Y., W.H. Brissette, P.D. Lira, et al., Impaired invariant chain degradation and antigen presentation and diminished collagen-induced arthritis in cathepsin S null mice. Immunity, 1999. **10**(2): p. 207-17.
22. Shi, G.P., J.A. Villadangos, G. Dranoff, et al., Cathepsin S required for normal MHC class II peptide loading and germinal center development. Immunity, 1999. **10**(2): p. 197-206.

APPENDIX CIRRICULUM VITAE OF PRINCIPAL INVESTIGATOR

UNIVERSITY OF PENNSYLVANIA - SCHOOL OF MEDICINE

Curriculum Vitae

June 2000

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Education:

1971-1975	B.A.	Kalamazoo College (Chemistry)
1975-1977	M.S.	Harvard University (Chemistry)
1977-1981	Ph.D.	Harvard University (Chemistry)
1983-1987	M.D.	University of Mississippi School of Medicine

Postgraduate Training and Fellowship Appointments:

1981-1982 Senior Scientist, Monsanto Company, St. Louis, MO.
1982-1987 Res. Associate, Dept. of Biochemistry, Univ. Miss. School of Medicine, Jackson, MS.
1987-1988 Intern in Medicine, University of Michigan Hospitals, Ann Arbor, MI
1988-1989 Residency in Medicine, University of Michigan Hospitals, Ann Arbor, MI
1989-1992 Hematology/Oncology Fellow, Univ. of Michigan Hospitals, Ann Arbor, MI

Military Service: None

Faculty Appointments:

1981-1982 Instructor, St. Louis Community College
1992-1993 Lecturer In Internal Medicine, Hematology/Oncology, University of Michigan.
1993-1994 Instructor, Division of Hematology/Oncology, University of Pennsylvania.
1994-pres. Ann B. Young Assistant Professor of Cancer Research, Division of Hematology/Oncology, Department of Medicine, University of Pennsylvania.

Hospital and Administrative Appointments:

1992 Admissions Committee, University of Michigan School of Medicine.
1992-1993 Home Infusion Service, Experimental Therapeutics Grant Review Committee. University of Michigan School of Medicine
1993 Scientific Retreat Committee, Institute for Human Gene Therapy, University of Pennsylvania.
1994-pres. Director of Cancer Gene Therapy Program, Institute for Human Gene Therapy, University of Pennsylvania.
1993-1998 Co-Director, Gene Therapy Program, The University of Pennsylvania Cancer Center
1999-pres. Director, Gene Therapy Program, The University of Pennsylvania Cancer Center

Specialty Certification:

1990 Board Certified, American Board of Internal Medicine
1996 Board Certified, Hematology

1994 Board Eligible, Medical Oncology

Licensure:
Michigan (1989-1996) Pennsylvania (1993-2000)

Awards, Honors and Membership in Honorary Societies:
1972-1975 Heyl Fellowship In Science, Kalamazoo College
1975 Honors Thesis, Kalamazoo College
1992-1995 Merck-American Fed. for Clinical Research, M.D./Ph.D. Postdoctoral Fellowship
1994-pres. Anne B. Young Assistant Professor for Cancer Research, July 1, 1994.
1995-1996 Measly Fellowship Award
1998 University of Pennsylvania Nominee for Rita Allen Award.

Memberships in Professional and Scientific Societies:]
Local Societies:
Philadelphia Cancer Research Association
Pennsylvania Chapter of the American Chemical Society
National Societies:
American Association for the Advancement of Science
American Federation of Clinical Research
American Association for Cancer Research
American Chemical Society
The Brain Tumor Society
American Society of Gene Therapy
National Scientific Committees

ECOG, Gene Therapy Committee, member	1996-present
NIH, NCI PO1 Review, Boston, MA	6/25-27/95
US Army Breast Can. Res. Program, Ad hoc reviewer	11/13-15/95
Breast Cancer Research Program, University of CA	1996-1998
NCI RFA Review Committee, Ad hoc reviewer	6/11-13/96
NIH, Neurosciences 3 Study Section, Ad hoc reviewer	6/26-28/96
NIH, NCI PO1 Review, New York,	7/7-9/96
NIH, NCI, Medicine Branch, Ad hoc reviewer, Wash. D.C.	9/10-12/96
NIMH PO1 Review, Washington, DC. Ad hoc reviewer,	12/96
NIH, NCI Ad hoc Reviewer	6/30/97
State of Massachusetts Breast Cancer Program	1997, 1998, 2000
North American Brain Tumor Consortium (NABTC) and New Approaches to Brain Tumor Therapy (NABTT) consortium multigroup glioma gene therapy clinical trial. Data and Safety Monitoring Committee, Chairman	1998-present
External Reviewer NCI PO1, Massachusetts General Hospital	5/98
NIH, NCI PO1 Review, Los Angeles,	7/27-29/98
State of Massachusetts Breast Cancer Program	10/24-25/98
NCI, Subcommittee D "Clinical Research Studies"	11/30-12/1/98
US Army Ovarian Cancer Study Section	1/20/99-1/22/99
NCI, Subcommittee D "Clinical Research Studies"	4/14-5/99
NCI, RAID Review	3/31/99-4/1/99
NIH, Career Development Award Review	6/21-22/99
NCI, Ovarian Cancer Spore Grants Review	6/27-29/99
NIH, NCI PO1 Review, Durham, NC	1/7/00-1/8/00
National Gene Vector Laboratories (NIH), Scientific Review Board	2000-
NIH, NCI, Special Emphasis Study Section in Clinical Oncology	4/00 – present
NCI, RAID Review	10/1/00

Editorial Positions:

Scientific Advisor, Education Committee, Pennsylvania Biotechnology Association, State College, PA 1995
Cancer Gene Therapy, Editorial Board, Simon & Schuster Publisher 1996-present
Gene Therapy, Editorial Board, Stockton Press. 1999-present
Current Gene Therapy, Editorial Board 2000- present
Ad hoc reviewer for:
Human Gene Therapy, Journal of Immunology, Cancer Research, Journal of Virology, American Journal of Gastroenterology, Gastroenterology, Gene Therapy, Nature Medicine, Annals of Neurology, Cancer Gene Therapy, Proc. Nat'l Acad. Sciences, DNA and Cell Biology, J. Organic Chemistry. J. Nuclear Medicine.

Academic Committees at the University of Pennsylvania and Affiliated Hospitals:

Clinical Trials Scientific Review and Monitoring Committee, UPCC 1996-1999
University of Penn. General Clinical Research Center Internal Review Committee 1996-97
Faculty Grievance Commission 1997-2000
Molecular Life Sciences Advisory Committee 1998-present
Vagelos Scholars Advisory Committee 1998-present
Short Term Experience in Research Advisory Committee 1999-present

Major Teaching and Clinical Responsibilities at the University of Pennsylvania (last 3 yrs):

1993-1999	Attending Physician, Oncology & Hematology Services, Hospitals of the University of Pennsylvania.
1994-1999	Attending Physician, Oncology & Hematology Services, Philadelphia Veterans Administration.
1996, 1998, 1999	Human Biology (Biology 6)
1996	Critical Care Nurse Practitioner Course, "Hematology in the Critical Care Setting"
1995-1999	Selected Topics in Chemistry (Chemistry 700)
1996-1999	The Molecular Basis of Gene Therapy, (CAMB 610)
1994-2000	Medicine 101C, Differential Diagnosis
1997-1999	Introduction to Gene Therapy (CAMB 610, Fall)
1999, 2000	Advanced Seminar in Cancer Gene Therapy (CAMB 633, Spring 1999) Course Director
1997	Wistar Cancer Biology Graduate Student Seminar
1997, 1998	Cancer Biology and Genetics Course (Pathology, Fall)
1998, 1999	Topics in Cancer Pharmacology (PHARM, Fall 1998, 1999)
1999, 2000	Cancer Pharmacology 560
2000	Ethics of Human Subjects Research, Medical School Cirriculum 2000
2000-2001	Introduction to Anatomy and Physiology (BSTA 510), A curse for Biostatistics graduate students

Lectures by Invitation:

October 19, 1992	"Inhibition of NF-kB by double-stranded oligonucleotides" - I.C.R.F., London, England.
October 25,1993	"Immunotherapy of Breast Cancer by B7 Gene Transfer", Institute for Human Gene Therapy Retreat, Tamiment, PA.
October 30, 1994	"Treatment of Advanced CNS Malignancy with Recombinant Adenovirus HSVtk", Institute for Human Gene Therapy Retreat, Absecon, NJ
January 11, 1995	"Adenovirus Vectors for the Treatment of Brain Tumors", BioEast Conference, Washington DC.
March 10, 1995	"Cancer Gene Therapy", Combined Science Seminar Series, Medical College of Pennsylvania and Hahnemann University, Philadelphia, PA.
April 22, 1995	"Adenoviral Vectors for the Treatment of CNS Tumors", 3rd International Conference on Biologic Therapy of Cancer, Munich, Germany.
April 25, 1995	"Gene Therapy", Medical Grand Rounds, Doylestown Hosp., Doylestown, PA.
May 10, 1995	"Vectors for Cancer Gene Therapy", The Second Symposium of the Philadelphia Cancer Research Association, "Approaches to Active Immunotherapy of Cancer", Thomas Jefferson Univ., Philadelphia, PA.
May 26, 1995	"Adenovirus-Mediated Cancer Gene Therapy", Univ.of North Carolina, Hematology and Oncology Research Seminar Series. Chapel Hill, NC.

June 9, 1995	"Adenovirus Mediated Gene Transfer for the Treatment Primary of CNS Malignancy" International Conference on Gene Therapy of CNS Disorders, Philadelphia, PA.
June 14, 1995	"Replication Competent Adenovirus Safety Issues" , Food and Drug Administration, International Conference on Viral Safety and Evaluation of Viral Clearance from Biopharmaceuticals Products. Bethesda, MD.
Sept. 21, 1995	"Clinical Aspects of Cancer Gene Therapy", Pennsylvania Oncologic Society Annual Meeting, Seven Springs, PA.
October 1, 1995	"Treatment of Primary CNS Tumors with Adenovirus Mediated Gene Transfer," The GAAC Meeting on Gene Therapy, Seeon, Germany.
January 18, 1996	"Adenoviral-Mediated Therapy of Brain Tumors", The Preuss Foundation Meeting on Gene Therapy for CNS Malignancies, Salk Institute, La Jolla, CA.
February 1, 1996	"Cancer Gene Therapy", Cooper Medical Center, Department of Medicine Grand Rounds, Camden , NJ.
April 17, 1996	"Gene Therapy", The Estelle Lasko Memorial Lecture, The Twenty-fourth Annual Chester County Cancer Conference, Chester County Hospital, West Chester, PA
April 19, 1996	"Gene Therapy for Inherited and Acquired Diseases", Genetics in the Cause and Treatment of Malignancies Conference, Sacred Heart Hospital, Allentown, PA.
May 13-7, 1996	"Laboratory and Clinical Approaches to Cancer Gene Therapy" 1996 Short Course in Cancer Biology, University of Nebraska Medical Center, Omaha, NE.
June 15, 1996	"Advances in Gene Therapy", The Coalition for Internal Medicine 1996 Scientific Meeting, Hershey, PA.
June 21, 1996	"Gene Therapy: Its Real, It Works and Its Coming to Your Practice," Grand Rounds, North Penn Hospital, Lansdale, PA.
July 11, 1996	"Cancer Gene Therapy" Shering-Plough Corporation, Kenilworth, NJ.
Nov. 14, 1996	"Adenoviral Vectors for Cancer Gene Therapy" Fifth International Symposium on Cancer Gene Therapy, San Diego, CA
Jan. 9, 1997	"Adenoviral Vectors for the Gene Therapy of Cancer", Wayne State University, Center for Molecular Medicine and Genetics, Detroit, MI
March 7, 1997	Gene Therapy for Gliomas and Colon Cancer, University of South Carolina, Department of Microbiology, Charleston, SC
April 25, 1997	"Colon Cancer Vaccines", Megabios Corporation, Burlingame, CA
May 11, 1997	"Methods of Gene Delivery", Plenary Session, American Society of Transplant Physicians, Chicago, IL
Aug. 7, 1997	"Gene Therapy of Malignant Gliomas" Cancer Section, Gorden Conference, Newport, RI.
Sept. 22, 1997	"Malignant Glioma Gene Therapy ", Rhome Poulenc-Roher, Collegeville, PA.
Oct. 20, 1997	"Experimental Therapies for Malignant Gliomas", Pathology Grand Rounds, Suburban General Hospital, Norristown, PA
March 13, 1998	"Gene Therapy Strategies for Malignant Glioma Therapy", Contemporary Concepts in Brain Tumor Therapy: From Genes to Patient Care Conference, Conshohocken, PA
March 28, 1998	"Phase I Trial of Gene Therapy for Primary Brain Tumors", Cerebral Vascular Biology 1998 Conference, Portland (Lincoln), OR.
June 29, 1998	"Phase I Trial of Gene Therapy in Primary Brain Tumors", American Society of Gene Therapy, Seattle, WA.
April 28, 1998	New Developments in Cancer Gene Therapy", Hematology/Oncology Research Conference, Children's Hospital of Philadelphia, Philadelphia, PA
August 18, 1998	"New Developments in Cancer Gene Therapy", Grand Rounds, Chestnut Hill Hospital, Philadelphia, PA
May 16, 1999	"Cancer Gene Therapy: Clinical Trials and Their Scientific Basis", American Society of Clinical Oncology Meeting, Atlanta GA.
June 12, 1999	"mEGP Blocks Class II Antigen Presentation" American Society of Gene Therapy, Washington D.C.
June 18, 1999	"Imaging Cancer Gene Therapy with PET" 25th Annual Pendergrast Symposium, Department of Radiology, University of Pennsylvania, Philadelphia, PA
Sept. 29, 1999	Gene Therapy: Applications for Brain Tumors and Other Malignancies" New York Medical College, Valhalla, NY

Oct. 19,1999	"Mouse EGP Inhibits Antigen Presentation in Dendritic Cells: A New Molecular Pathway for Tumor-Mediated Immune Suppression", University of North Carolina Cancer Center Grand Rounds, Chapel Hill, NC
Oct. 22, 1999	Clinical Infection Control in Gene Therapy: Clinical Applications of Gene Therapy". University of Kentucky Medical Center, Lexington, KY.
Dec 17, 1999	"Gene Therapy for Malignant Gliomas and other Cancers, Grand Rounds, Moffitt Cancer Center, University of South Florida, Tampa, FL
January 7, 2000	Mouse Epithelial Glycoprotein: A Tumor Antigen That Inhibits Antigen Presentation" Surgery Grand Rounds, Memorial Sloan-Kettering Cancer Center, New York, NY
January 8, 2000	"Will the Re-Engineering of Human Beings Re-Engineer Human Nature" The University of Pennsylvania Humanities Forum, Philadelphia, PA.
April 12, 2000	"Gene Therapy for Malignant Gliomas", University of Florida Cancer Center Grand Rounds, Gainesville, FL
April 28,2000	"The Current Status of Gene Therapy for Brain Tumors" Oregon Health Sciences University, 4th Annual Conference on Blood-Brain Barrier Delivery, Timberline Lodge, Government Camp, Oregon.
June 20, 2000	"New Developments in Cancer Gene Therapy", Department of Medicine Grand Rounds, Oregon Health Sciences University, Portland, OR.
July 26, 2000	"How tumors avoid being seen: a tumor associated antigen that blocks class II mediated antigen presentation" Hematology/Oncology Division Research Conference, University of Michigan Medical Center, Ann Arbor, MI

Organizing Roles In Scientific Meetings

American Society of Gene Therapy Annual Meeting, 1998, 1999
Society of Neuro-Oncology Annual Meeting 1998

Bibliography:

Research Publications, peer reviewed

Wender, P.A. and Eck, S.L. : Organobiscuprates. A Single-Step Spiroannelation Method. Tetrahedron Letters, 18: (14) 1245-1248, 1977.

Wender, P.A., and Eck, S.L.: The Olefin Metathesis/Transannular Ene Sequence: A Method for the Stereo-controlled Synthesis of Trans-Decalin Derivatives. Total Synthesis of Warburganal. Tetrahedron Letters, 23:(18) 1871-1874, 1982.

Wilson, V. E., Eck, S.L., and Bates, E.R.: Diagnosis and Management of Acute Myocardial Infarction Complicating Systemic Lupus Erythematosis. Chest, 101:420-424, 1991.

Eck, S.L., Morse J.M., Janssen, D.A., Emerson, S.G., and Markovitz, D.M.: Angioedema Presenting as Gastrointestinal Symptoms. Am. J. Gastro., 88:436-439, 1993.

Eck, S.L., Perkins, N.D., Carr, D.P., and Nabel, G.J.: The Inhibition of Phorbol Ester Induced Cellular Adhesion by Competitive Binding of NF-kB In Vivo. Mole. Cell. Biol., 13: 6530-6536, 1993.

Smythe, W.R., Kaiser, L.R., Hwuang, H.C., Amin, K.M., Pilewski, J.M., Eck, S.L., Wilson, J.M., and Albelda, S.M.: Successful Adenovirus-Mediated Gene Transfer in an In Vivo Model of Human Malignant Mesothelioma. Ann Thoracic Surg. 57:1395-401, 1994.

Smythe, W.R., Hwuang, H.C., Amin, K.M., Eck, S.L., Davidson, B.L., Wilson, J.M., Kaiser, L.R., and Albelda, S.M.: Use of Recombinant Adenovirus to Transfer the HSV-Thymidine Kinase Gene to Thoracic Neoplasms: An Effective In Vitro Drug Sensitization System. Cancer Res. , 1994, 54:2055-2059.

Smythe, W.R., Hwuang, H.C., Amin, K.M., Eck, S.L., Davidson, B.L., Wilson, J.M., Kaiser, L.R., and Albelda, S.M.: Treatment of Experimental Human Mesothelioma Using Adenovirus Transfer of the Herpes Simplex-Thymidine Kinase Gene. Annals of Surgery. 1995,222(1):78-86.

Coughlin, C., Wysocka, M., Kurzawa, H., Lee, W., Trinchieri, G., Eck, S.L.: B7-1 and IL-12 Synergistically Induce Anti-Tumor Immunity. Cancer Research 55:4980-87, (1995).

Eck, S.L., Alavi, J.B., Alavi, A., Davis, A. Hackney, D.B., Judy, K.D., Mollman, J., Phillips, P. C., Wheeldon, E.B. and Wilson, J.M., Treatment of Advanced CNS Malignancy with the Recombinant Adenovirus H5.010RSV*TK*: A Phase I Trial, Human Gene Therapy 1996)7: 1469-1486.

Smith, J.G., Raper, S.E., Wheeldon, E.B.,Hackney, D., Judy, K., Wilson, J.M., and Eck, S.L. Intracranial administration of adenovirus expressing HSVTK in combination with ganciclovir produces a dose dependent, self-limiting inflammatory response. Human Gene Therapy. 1997, 8(8):943-954.

Behbakht, K., Benjamin, I., Chiu,H.-C., Eck, S.L., Van Deerlin, P.G., Rubin, S.C., and Boyd, J., Adenovirus-Mediated Gene Therapy of Ovarian Cancer in a Mouse Model, Am. J. Obstet. Gynecol. 1996, 175, 1260-1265.

Zheng, M., Cerniglia, G.L., Eck, S.L., and Stevens, C.W. High-Efficiency Stable Gene Transfer of Adenovirus into Mammalian Cells Using Ionizing Radiation. Human Gene Therapy 1997, 8(9)1025-1032.

Basak S. Speicher D. Eck S. Wunner W. Maul G. Simmons MS. Herlyn D. Colorectal carcinoma invasion inhibition by CO17-1A/GA733 antigen and its murine homologue. Journal of the National Cancer Institute. 90(9):691-7, 1998

Smith, J.G. and S .L. Eck, S.L. Molecular characterization of an adenoviral vector resulting from both homologous and non-homologous recombination. Cancer Gene Therapy 1999 6(5): 475-481.

H. K. E. Boxhorn, M. Jost, U. Rodeck, S. Ethier, S. L. Eck. Human breast cancer cell lines inhibit the proliferation of human peripheral blood mononuclear cells by PGE2 and other immunosuppressive factors 1999 (submitted in revision)

H.K.E. Boxhorn, J.G .Smith, Y. Chang, Dupont G., W. M.F. Lee, U. Rodeck, L. Turka, S. L. Eck. Adenoviral transduction of melanoma cells with B7-1: anti-tumor immunity and immunosuppressive factors. Cancer Immunology and Immunotherapy 1998 46:283-292.

M. Nesbit, H.K.E. Nesbit, J. Bennett. T. Andl, M.-Y. Hsu, E. Dejesus, M. McBrian, A.R. Gupta, S.L. Eck and M. Herlyn.: Basic fibroblast growth factor induces a transformed phenotype in normal human melanocytes. Oncogene, 1999, 18: 6469-6476.

R. Gutzmer, S. Sutterwala, E. Behrens, L. Wei, M. Marks and S. L. Eck: Mouse Epithelial Glycoprotein blocks Class II restricted Antigen Presentation in Dendritic Cells (submitted 2000).

Alavi, J.B., Alavi, A., Davis, A. Hackney, D.B., Judy, K.D, Phillips, P. C., and Eck, S.L., Treatment of Advanced CNS Malignancy with the Recombinant Adenovirus Expressing HSVtk: The results of A Phase I Trial 1999, (in preparation).

R Hustinx, CY Shiue, HM Zhuang, G Shiue, D. McDonald, P. Lu, DY Chen, JG Smith, A Alavi, SL Eck.: Monitoring Herpes Simplex Virus Thymidine Kinase Gene Transfer To Tumors With ^{18}F-FHPG and PET 1999 (submitted).

MA Schnell, JV Hughes, J Barsoum, J Green, G-P Gao, D Hackney, E Glover, L, D. Chen, JM Wilson, S.L. Eck: Intracerebral Administration Of An E-1, E-3 Deleted Adenovirus With the Interferon-β Gene In Mice And Non-Human Primates. 2000 (in preparation)

Y Chen, K. Song, SL Eck and Y Chen: An Intra-Peyer's Patch Gene Transfer Model for Studying Mucosal Tolerance: Distinct Roles of B7 and Interleukin-12 in Mucosal T Cell Tolerance. J. Immunology (In press).

ND Doolittle, CP Anderson, WA Bleyer, JG Cairncross, T Cloughesy, SL Eck, P Guastadisegni, WA Hall, LL Muldoon, SJ Patel, D. Peereboom, T.Siegal, EA Neuwelt: Importance of Dose-Intensity in Neuro-Oncology Clinical Trials, Neuro-Oncology, 2000: (submitted)

Research Publications, non-peer reviewed

Eck, S.L. and Nabel, G.J. : Antisense Oligonucleotides for Therapeutic Intervention. Current Opinion in Biotechnology, 2:897-904, 1992

Wysocka, M., Coughlin, C.M., Kurzawa, H.L., Trinchieri, G., Eck, S.L. and Lee, W.M., Mechanism of the induction of anti-tumor immunity by B7.1 and interleukin-12. Annals of the New York Academy of Sciences, 1996. 795:429-33.

R. Hustinx, S. Eck and A. Alavi: Potential Applications of PET Imaging in Developing Novel Cancer Therapies, J. Nucl. Medicine 1999 , 40(6):995-1002

Recent Published Abstracts

Tani, M., Shy, M., Eck, S.L., Scherer, S., Shi, Y.-j. and Kamholtz, J.: Introduction of the lacZ Gene into Schwann Cells in vitro and in vivo Using an Adenoviral Vector. Peripheral Nerve Society, St. Paul Minnesota, June 12-16, 1994.

Eck, S.L., Smith, J., Wheeldon, E. Smith, D., Hackney, D., and Raper, S. Adenovirus-Mediated Gene Transfer of the HSV-TK gene for the Treatment of Primary CNS Malignancies. Third International Symposium on the Biological Therapy of Cancer. European Organization for Research and Treatment of Cancer and The National Cancer Institute, Munich, Germany April 19-22, 1995.

Hackney, D.B., Smith, J.G., Smith, D., and Eck, S.L. A dose-escalation toxicity study of Adenovirus-mediated Gene Transfer for the Therapy of Brain Tumors. 81st Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, IL. Nov. 26 -Dec 1. 1995. Radiology, 1995; 197(P):237

Rubin, S.C., Chiu, H.C., Benjamin, I., Eck, S.L., and Boyd, J. Adenovirus Mediated Gene Therapy of Ovarian Cancer. Society of Gynecologic Oncologists.

Basak, S., Zaloudik, J., Nesbit, M., Wunner, W., Eck, S., Bergsagel, P.L., and Herlyn, D. Mouse model of active immunotherapy against the human colon carcinoma (CC)-associated antigen (Ag) CO17-1A/GA733. AACR 87th Annual Meeting, Washington, D.C. April 20-24, 1996.

Alavi, J.B., Judy, K., Alavi, A., Hackney, D., Philips, P., Mollman, J. Pruitt, A. Recio, A. Wilson, J.M. Eck, S. L. Phase I Trail of Gene Therapy in Primary Brain Tumors. 1998 Proceedings of the American Society of Clinical Oncology. 17:379a .

Hustinx, R, Hackney, DB, Alavi, JB, Eck, SL, Judy, KD, Phillips, PC, Mollman J, , Smith, J, Pruitt, Alavi, A. Monitoring the response to gene therapy for malignant gliomas with FDG PET and MRI: preliminary results. American Society of Neuroradiology 36th Annual Meeting Proceedings, p. 226, 1998.

Hustinx, R, Hackney, DB, Benard, F. Alavi, JB, Eck, SL, Judy, KD, Phillips, PC, Alavi, A. Evaluation of Response to Gene Therapy for Malignant Gliomas with FDG PET Imaging and MRI. J. Nucl. Med., 39(5):255p, 1998.

Alavi, J.B., Judy, K., Alavi, A., Hackney, D., Philips, P., Smith, J., Pruitt A, Recio, A. Wilson, J.M. Eck, S. L. Phase I Trial of Gene Therapy in Primary Brain Tumors. Cerebral Vascular Biology Conference,1998

Boxhorn, H. K. E, U. Rodeck, R. Gutzmer, M. Jost, and S. L. Eck, (1999). "Human breast cancer derived PGE2 inhibits B7-1 induced T cell proliferation (abstract) American Association for Cancer Research Annual Meeting, Philadelphia, PA. April 10-14, 1999.

R. Gutzmer, E. Behrens, E. M. Maldonado, D. Herlyn and S. L. Eck, (1999). "Expression of the murine colon cancer antigen mEGP on dendritic cells abrogates their T cell stimulatory capacities" (abstract) American Association for Cancer Research Annual Meeting, Philadelphia, PA. April 10-14, 1999.

Editorials, Reviews, Chapters:

Eck, S. L. and J. M. Wilson, Somatic Gene Therapy. in Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 9th edition. 1995.

Weitzman, M.D., Wilson, J.M., Eck, S.L. Adenovirus Vectors in Cancer Gene Therapy, in The Internet Book of Gene Therapy: Cancer Therapeutics. R.E. Sobol and K.J. Scanlon, eds. Appleton and Lange, 1995.

Alavi, J.B., J.S. Smith, and Eck, S.L. Adenoviral Gene Therapy Of Central Nervous System Tumors, in Clinical Trials of Genetic Therapy with Antisense DNA and DNA Vectors, E. Wickstrom, ed. Marcel Dekker, Inc, NY 1998.

S. L. Eck, Future Directions for the Treatment of Colorectal Carcinoma, in Hematology/Oncology Clinics of North America, W.B. Saunders, Co. 1997, Vol 11(4):795-810.

Alavi, J.B. and Eck, S.L., Gene Therapy of Malignant Gliomas, in Hematology/Oncology Clinics of North America: Gene Therapy, S.L. Eck, Editor. 1998, W.B. Saunders, Philadelphia p 617-629.

H.K.E. Boxhorn, and Eck, S.L., Gene Therapy of Breast Cancer, in Hematology/Oncology Clinics of North America: Gene Therapy, S.L. Eck, Editor. 1998, W.B. Saunders, Philadelphia, p 665-675.

Books

Eck, S.L., editor Hematology/Oncology Clinics of North America: Gene Therapy, 1998, W.B. Saunders, Philadelphia.